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The role of tissue damage in whiplash associated disorders: Discussion paper 1

Michele Curatolo, MD*, **Nikolai Bogduk, MD****, **Paul C. Ivancic, PhD*****, **Samuel A. McLean, MD†**, **Gunter P. Siegmund, PhD††,†††**, and **Beth Winkelstein, PhD††††**

*University Department of Anesthesiology and Pain Therapy, University of Bern, Inselspital, 3010 Bern, Switzerland, Phone: ++41-31-632 2483, Fax: ++41-31-632 3028, michele.curatolo@insel.ch

**University of Newcastle, Newcastle Bone and Joint Institute, Royal Newcastle Centre, Newcastle, New South Wales, Australia

***Biomechanics Research Laboratory, Department of Orthopaedics and Rehabilitation, Yale University School of Medicine, 333 Cedar St., P.O. Box 208071, New Haven CT 06520-8071, USA

†Departments of Anesthesiology and Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA 27599-7010

††MEA Forensic Engineers & Scientists, 11-11151 Horseshoe Way, Richmond, BC, Canada V7A 4S5

†††School of Human Kinetics, University of British Columbia, 210-6081 University Blvd, Vancouver, BC, Canada V6T 1Z1

††††Departments of Bioengineering & Neurosurgery, University of Pennsylvania, 240 Skirkanich Hall, 210 S. 33rd St., Philadelphia, PA 19104-6392

Abstract

STUDY DESIGN—Non-systematic review of cervical spine lesions in whiplash-associated disorders (WAD).

OBJECTIVE—To describe whiplash injury models in terms of basic and clinical science, to summarize what can and cannot be explained by injury models, and to highlight future research areas to better understand the role of tissue damage in WAD.

SUMMARY OF BACKGROUND DATA—The frequent lack of detectable tissue damage has raised questions about whether tissue damage is necessary for WAD and what role it plays in the clinical context of WAD.

METHODS—Non-systematic review.

Correspondence to: Michele Curatolo.

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RESULTS—Lesions of various tissues have been documented by numerous investigations conducted in animals, cadavers, healthy volunteers and patients. Most lesions are undetected by imaging techniques. For zygapophysial (facet) joints, lesions have been predicted by bioengineering studies and validated through animal studies; for zygapophysial joint pain, a valid diagnostic test and a proven treatment are available. Lesions of dorsal root ganglia, discs, ligaments, muscles and vertebral artery have been documented in biomechanical and autopsy studies, but no valid diagnostic test is available to assess their clinical relevance. The proportion of WAD patients in whom a persistent lesion is the major determinant of ongoing symptoms is unknown. Psychosocial factors, stress reactions and generalized hyperalgesia have also been shown to predict WAD outcomes.

CONCLUSION—There is evidence supporting a lesion-based model in WAD. Lack of macroscopically identifiable tissue damage does not rule out the presence of painful lesions. The best available evidence concerns zygapophysial joint pain. The clinical relevance of other lesions needs to be addressed by future research.

Keywords

whiplash; Cervical spine; tissue damage; Facet Joint; nociception; Psychosocial factors; central sensitization

INTRODUCTION

Tissue damage frequently cannot be detected in patients with whiplash-associated disorders (WAD). This leads to the question of whether a lesion, responsible for a nociceptive focus, exists and what importance it may have in the determination of symptoms. Furthermore, debate remains as to whether tissue injury is necessary or sufficient to initiate and/or maintain WAD.

In this review, we describe current whiplash injury models in terms of their basic and clinical science. The literature cited was based on the personal libraries and publications of the authors. In this context, there is no pretence of covering the pathophysiology of WAD comprehensively, and consequently mechanisms other than a biomechanical lesion are only marginally mentioned. Our goal is to summarize what can and cannot be explained by injury models, and to guide future research that is needed to better understand the role of tissue damage in WAD.

BIOMECHANICAL CONTEXT FOR TISSUE INJURY

KINEMATICS, KINETICS AND BIOMECHANICS

To better understand whiplash injuries and their prevention, bioengineers have pursued research in two principal domains. Simulated automobile collisions have been performed to predict the presence, timing, and severity of tissue damage and to determine the effects of injury prevention systems. Central to both domains is the quantification of whiplash-induced neck kinetics, i.e. dynamic loads transferred to the neck during the collision, and kinematics which includes intervertebral motions and tissue strains. While some autopsy¹ and cadaveric studies^{2,3} have used post-collision anatomical dissection to identify macroscopic neck lesions, other studies defined the potential for tissue damage as non-physiologic neck motions during the collision-exposure.^{4,5}

Kinematics and kinetics have been studied using crash dummies, human cadavers, human volunteers, and computer models. Collectively these studies have shown that during rear-end collisions the cervical spine initially undergoes a horizontal shear or retraction.^{6–8} Continued

retraction accelerates the head and ultimately the cervical spine into extension, followed by acceleration forward and into flexion as a result of head restraint interaction. Total movement of the head and neck largely remains within physiologic limits.⁸ However, abnormal motions may occur at one or more spinal levels, particularly during the S-shape phase of neck motion, which consists of flexion at the upper spinal levels and extension at the lower levels.^{7,9,10} Studies in cadavers and in normal volunteers have consistently shown that movements of the lower and upper cervical segments during a motor vehicle collision can exceed physiologic limits.^{11–13} Abnormal neck postures or axial rotation at the time of the collision increase the risk of structural injury.^{14–17}

Evident from this research is that whereas the responses of occupants conform to a general pattern, the magnitudes of the cervical spine dynamics, and their timing, vary for the same subject in different vehicles,^{18,19} and between different subjects in the same vehicle,⁸ even if the collision severity remains constant. This response variability stems from a diverse range of collision-related, vehicle-related and human-related factors, and exposes the cervical tissues to a wide range of forces and strains. Even greater variability exists in the tolerance to injury of specific cervical tissues,^{14,20,21} and the particular combination of tissue exposure and tissue tolerance is hypothesized to determine the genesis, or not, of a tissue lesion in a particular crash.

INJURY PREVENTION

The 1969 Federal Motor Vehicle Standards, FMVSS 202,²² required automobiles manufactured in USA to incorporate head restraints. However, the standards did not establish requirements for head restraint position. Epidemiological studies found that these traditional head restraints were either ineffective in preventing neck injuries^{23,24} or provided up to only 20% reduction in whiplash injury risk.^{25–27}

Contemporary approaches to prevention of neck injuries in rear-end collisions have focused on absorbing collision energy and reducing neck motions by modifying seat and head restraint designs.^{28,29} Field data evaluating the effectiveness of newer anti-whiplash seat and head restraint designs have shown wide variations. One new seat design initially showed no effect on injury rates, whereas another reduced the risk by 75%.^{29,30} The most recent assessment of their effectiveness, however, suggests an average reduction in permanent impairment of about 50% across the three main anti-whiplash seats installed in the fleet.³¹ These reductions indicate that cervical tissues exposed to lower forces and strains have a lower risk of injury, a finding suggesting that a tissue lesion is responsible for many whiplash injuries.

Some limitations apply to the literature on seat and head restraint effectiveness. Some studies were performed with involvement of the manufacturers,^{29,32} with consequent potential conflict of interest. Furthermore, some of the effectiveness studies rely on insurance rather than clinical definitions of injury, and the effect of any bias introduced by these definitions remains unclear.

LESIONS

In cadaveric and post-mortem studies a spectrum of tissue damage has been demonstrated, including: strains beyond physiologic limits in the zygapophysial joint capsules and anuli fibrosi; partial or complete ruptures of capsules, ligaments, and anuli fibrosi; intra-articular contusions; intra-articular fractures; and transarticular synovial joint fractures.^{1,3,14,21,33} There is growing evidence from in-vivo animal models of these tissues that their injury can lead to modifications in tissue properties, nociceptor activation, immediate and sustained

dysfunction in afferents and spinal neurons, neuroplastic changes and pain.^{34–41} A summary of the current injury models and their development state is presented in table 1.

ZYGAPOPHYSIAL JOINTS AND CAPSULES

Although animal studies have focused on various tissues, the greatest body of literature focuses on the capsule of the zygapophysial (facet) joint. In particular, independent studies in different species (rats and goats) provide corroborative evidence supporting the biomechanical findings of injury of the facet capsule derived from the human cadaver and volunteer studies. For example, for comparable maximum principal strains (ranging between ~15–50%) applied to the facet capsular ligament, afferents become saturated and persistent pain is induced.^{36,42,43} Those same loading scenarios are also associated with production of collagen fiber disorganization, axonal swelling and altered morphology in the ligament, and permanent modification in the neuronal signaling in the spinal cord.^{38–40,44,45}

Using an animal model, it was also demonstrated that removing the contribution of the facet capsule prior to loading the joint resulted in no pain production and reduced spinal glial activation,⁴⁶ further supporting this tissue's involvement in WAD. Further, NSAID treatment delivered to the joint following both injury and pain development extinguished the pain.⁴⁷

Of particular interest for WAD is the consistent finding that all of the pathologies listed above are induced in the *absence* of grossly observable evidence of a rupture or tear. Of even greater interest is the finding that higher tissue loading leading to complete and observable capsule rupture results in no prolonged afferent discharge and no persistent pain.⁴⁶ These physiological findings present a stark discourse with the biomechanical tenet that more severe loading is more detrimental. They also challenge the belief that lesions that are not clinically detectable cannot be relevant for patients' symptoms.

These observations provide pivotal basic-science evidence that cervical zygapophysial joints can be damaged by whiplash injury and can become sources of pain. They are also consistent with clinical evidence. Indeed, although the current medical imaging technologies do not have sufficient resolution to detect such subtle and small changes, the nociception that excessive capsular strain produces can be tested and detected in patients. Cervical medial branch blocks anaesthetize afferents from the zygapophysial joints.⁴⁸ If a patient has pain from some other source, such blocks should not relieve their pain. But a patient with pain stemming from a particular joint should be relieved of his pain if the nerves from that joint are anaesthetized. Crucial for the validity of such blocks is that they must be controlled, in order to reduce false-positive responses.⁴⁹

Studies using double-blind controlled medial branch blocks found that the prevalence of pain stemming from one or more zygapophysial joints was 60% (95% confidence interval (CI) 46–73%) and 54% (95% CI 40–68%) amongst patients with chronic neck pain after whiplash; 27% (95% CI 18–36%) of consecutive patients with neck pain and/or headache after whiplash had pain stemming from the joint C2-3.^{50–52} The segmental location of symptomatic joints is consistent with the location predicted by biomechanical studies: joints at C5-6 or C6-7 and at C2-3 are most commonly affected.^{13,53,54}

Once diagnosed, a treatment for zygapophysial joint pain is available. A placebo-controlled trial⁵⁵ and several observational studies with long-term follow-up^{56–58} have shown that percutaneous radiofrequency neurotomy can abolish chronic neck pain stemming from the zygapophysial joints in approximately 70% of treated patients.

ANTERIOR LONGITUDINAL LIGAMENTS AND DISCS

Tears of the anterior longitudinal ligament and rim lesions of the anterior annulus fibrosus have been produced in cadavers subjected to whiplash injuries³ and observed in post-mortem studies.^{1,33} During whiplash, strains in the annulus fibrosus of lower cervical discs can exceed physiologic limits.^{7,59} These observations provide a pathologic basis for tears of the anterior disc or the anterior longitudinal ligament being a source of nociception after whiplash injury. Theoretically, lesions of these anterior structures could evoke the same physiological responses that have been demonstrated for the cervical zygapophysial joints. However, this model has not yet been explored outside the cadaver. Nor has discogenic pain after whiplash injury been explored clinically. At present, there are no imaging techniques by which noxious strains of the anterior disc can be demonstrated in vivo. Provocation discography might be used to test for cervical discogenic pain, but its validity for detecting symptomatic tears has not been established. Appropriate techniques might be developed and applied if laboratory studies, in due course, provide convincing evidence that anterior lesions produce nociception in experimental animals.

DORSAL ROOT GANGLION

There is the potential for trauma to the nerve roots and dorsal root ganglion in the neck. Unlike studies of the spinal ligaments, neural impingement is challenging to investigate experimentally. In fact, cadaveric study requires measuring the space in the neural foramen and using that as a proxy for tissue injury.⁶⁰ While that cadaveric study suggests a potential mechanism by which nerve root impingement may occur, no study has addressed the specific relationship between decreased foraminal space and the nociceptive physiological responses.

Notwithstanding direct impingement, the cervical nerve roots and dorsal root ganglia are at risk for injury due to rapid changes in the canal pressure that can be established during rapid head and neck motions. Pressure gradients from blood flow resistance have been hypothesized to be generated in the central nervous system during rapid spinal motions, as can occur during whiplash.^{61,62} Although the vasculature surrounding the vertebral column regulates blood volume to accommodate any changes in spinal canal size, during rapid head/neck motions, resistance to blood flow can generate pressure gradients both inside and outside of the spinal canal.^{18,61–63} These gradients have been shown to induce plasma membrane breakdown of spinal ganglia nerve cells in an in-vivo porcine model of rapid head-neck extension.^{18,61,63}

Although suggesting a potential mode of injury to the cell bodies of the neurons, that collection of work provided no direct measure of pain and was not able to explain other types of painful injuries to the nerve root and/or the dorsal root ganglia. Nonetheless, it offers a potential mechanism by which neck, upper limb and/or shoulder girdle pain can result from nerve root injuries and trauma in the neck.

VERTEBRAL ARTERY

A recent retrospective analysis of 500 whiplash patients indicated that the incidence of cervical arterial dissections in this group was significantly higher than in the general population (1.6 vs. 0.0041%).⁶⁴ The onset of cerebrovascular symptoms may occur 4 to 12 months following the automobile collision. Altered blood flow rates in vertebral arteries of whiplash patients have been associated with chronic symptoms.⁶⁵

Vertebral artery injury may originate from an intimal tear, most commonly at C1-2, which is the primary site of cervical axial rotation.^{66–68} Coupled cervical spine extension and axial rotation beyond the physiologic limit has been hypothesized to cause vertebral artery

injury.⁶⁶ This hypothesis is supported by biomechanical research,¹⁶ which indicates that elongation-induced vertebral artery injury may occur due to non-physiologic coupled neck motions during an automobile collision. Coupled neck motions may occur due to an offset collision configuration and/or a rotated head posture at the time of the collision. Transient vascular compromise may be due to pinching of the vessel along a turn in its circuitous course, while a tear in the intimal layer may originate due to overstretching of the artery during the collision-exposure.

While some evidence of this tissue's injury mechanism has been demonstrated in the cadaver, no further exploration of this lesion has been undertaken. There is no validated diagnostic tool available to identify arterial dissections caused by whiplash, and these may be difficult to differentiate from those of the general population.

MUSCLES

Pain perceived at regions corresponding to muscles is common in WAD. Direct injury to muscles can occur from the imposed lengthening during reflex neck muscle activation in response to a crash. Biomechanically, muscle fascicle strains of 7% in the sternocleidomastoid muscle and 21% in the semispinalis capitis muscle have been predicted from human subject and modeling studies,^{4,69} and these strains are larger than those shown to cause muscle injury.^{70,71} Clinically, elevated levels of serum creatine kinase, a marker of muscle injury, have been recorded 24 hours, but not 48 hours, after whiplash injury in patients.⁷² Since pain in these patients lasted more than 3 months, these data suggest that lesions to the muscles following a whiplash exposure may be related to the acute rather than chronic phase of whiplash injury.

Some neuromuscular abnormalities of the cervical spine observed in whiplash patients, including repositioning error^{73,74} and altered range of motion,^{75,76} might also originate from injuries to cervical zygapophysial joint capsules, ligaments, or annular fibers.⁷⁷ Animal models have demonstrated that stimulation of spinal ligaments initiated spinal muscle activity.⁷⁸ Abnormal signals from mechanoreceptors of injured capsules, ligaments, or annular fibers may cause corrupted neck muscle response patterns and hinder proper neck proprioception of whiplash patients.⁷⁷ The neuromuscular control system may stiffen the injured neck to prevent further injuries, thus reducing active neck motion and causing painful muscle spasm. Direct insertion of the multifidus muscles onto the facet capsular ligaments of C4 through C7 may aggravate the lesion of an already injured capsule during otherwise normal head and neck movements.^{79,80} Also, reflex activation of the multifidus muscles during the crash may pull on the facet joint capsule and contribute to its initial insult.⁸¹

So far, no research has produced clinical evidence for a role of the muscles in the determinations of symptoms in WAD. It is largely recognized that the muscles can be areas of referred pain, the primary nociceptive focus being in another structure of the neck.⁸² To date, there is no validated diagnostic tool to identify muscles as the primary source of nociception.

CLINICAL CONTEXT

LESION

The demonstration of tissue damage refutes the proposition that damage cannot occur as a result of whiplash injury. Unfortunately, many of the candidate lesions demonstrated in the cadaver or animal models cannot be identified by clinically available diagnostic modalities. Plain radiography cannot detect tears in capsules or discs;^{1,3} and it lacks sensitivity for small fractures.¹ Small fractures may be detected by CT scanning, but concerted studies, using

high-resolution CT, have not been undertaken in patients with WAD to determine the prevalence of fractures in this population. In human cadavers undergoing rear-end impacts, CT was unable to reliably detect partial ruptures of the ligamentum flavum, annulus fibrosus, anterior longitudinal ligament, or capsular ligaments.³ Conventional magnetic resonance imaging has not revealed lesions in patients with WAD,^{83,84} but this failure may be due to limitations in the resolution of conventional devices and the imaging sequences used. The prospect remains that 3 Tesla devices, or their successors, might provide greater resolution to reveal currently elusive, but still clinically relevant lesions.

Zygapophysial joint pain is the one entity predicted by biomechanical studies that has been fully validated through animal studies, for which there is a valid diagnostic test, and for which there is a proven treatment that can abolish pain. Other candidate lesions have the potential to undergo similar translation from biomechanics to clinical practice, and become recognized as a patho-anatomic basis for WAD; but this process awaits the development, application, and validation of appropriate diagnostic and therapeutic techniques.

OTHER FACTORS

The severity of pain reported, and the disability that ensues is not exclusively a product of the tissue damage. Additional factors apply, such as the psychology and social context of the patient,^{85,86} whether or not they are believed,⁸⁷ how compensation systems treat them,⁸⁸ and central neuroplastic changes leading to hyperalgesia and allodynia.⁸⁹

Animal and human studies indicate that stress exposure may influence neurosensory processing.^{90,91} Based on this research, it can be hypothesized that some lesions may produce chronic pain only in individuals with a neurobiological “environment” vulnerable to sensitization. This hypothesis needs to be tested by future research. Animal studies that induce standardized lesions within different neurobiological milieus may provide new information about the interaction between lesion and environment in the development of persistent pain. Large clinical cohort studies examining genetic factors associated with whiplash development may also provide new mechanistic insights: if a genetic factor influencing the function of a particular biologic pathway is associated with WAD outcomes, this would provide evidence that the biologic pathway contributes to chronic pain development.

A challenging hypothesis is that a lesion is not necessary for persistence of symptoms. According to this hypothesis, in some patients the initial lesion may play only a transient initiating role, and instead the neurobiological environment that facilitates sensitization of nociceptive pathways or the psychosocial context may be the dominant factors determining symptom perpetuation. Unfortunately, for many patients with persistent neck pain following motor vehicle collision, no specific lesion driving symptom persistence can be identified using currently available technology. In this setting, opinions differ regarding the proportion of patients in whom an undetectable persistent lesion is present and driving ongoing symptoms. As engineers, basic scientists and clinicians continue to investigate the challenging problem of whiplash prevention, diagnosis and treatment, advances in all of these areas are needed to more completely address this issue. Fortunately, the current landscape includes a growing number of knowledgeable whiplash researchers and practitioners, who are well-past the era when the pain and suffering of whiplash patients was discounted and dismissed. The suffering is real; the search for the causes must continue.

KEY POINTS

1. There is evidence supporting a lesion-based model in whiplash associated disorders (WAD).

2. Zygapophysial joint pain is the one entity predicted by biomechanical studies, validated through animal studies, and for which there is both a valid diagnostic test and a proven treatment.
3. Other candidate lesions have the potential to undergo similar translation from biomechanics to clinical practice, but the evidence is not yet available.
4. The proportion of WAD patients in whom a persistent lesion is the major determinant of ongoing symptoms is unknown; psychosocial factors, stress reactions and generalized hyperalgesia have also been shown to predict WAD outcomes.

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REFERENCES

1. Jonsson H Jr, Bring G, Rauschnig W, et al. Hidden cervical spine injuries in traffic accident victims with skull fractures. *J Spinal Disord.* 1991; 4:251–263. [PubMed: 1802155]
2. Ivancic PC, Pearson AM, Panjabi MM, et al. Injury of the anterior longitudinal ligament during whiplash simulation. *Eur Spine J.* 2004; 13:61–68. [PubMed: 14618382]
3. Yoganandan N, Cusick JF, Pintar FA, et al. Whiplash injury determination with conventional spine imaging and cryomicrotomy. *Spine.* 2001; 26:2443–2448. [PubMed: 11707708]
4. Vasavada AN, Brault JR, Siegmund GP. Musculotendon and fascicle strains in anterior and posterior neck muscles during whiplash injury. *Spine.* 2007; 32:756–765. [PubMed: 17414909]
5. Ivancic PC, Xiao M. Cervical spine curvature during simulated rear crashes with energy-absorbing seat. *Spine J.* 2011; 11:224–233. [PubMed: 21377605]
6. Grauer JN, Panjabi MM, Cholewicki J, et al. Whiplash produces an S-shaped curvature of the neck with hyperextension at lower levels. *Spine.* 1997; 22:2489–2494. [PubMed: 9383854]
7. Panjabi MM, Pearson AM, Ito S, et al. Cervical spine curvature during simulated whiplash. *Clin Biomech (Bristol. Avon).* 2004; 19:1–9.
8. Siegmund, GP.; King, J.; Lawrence, JM. Head/neck kinematic response of human subjects in low-speed rear-end collisions. 41st Stapp Car Crash Conference; 1997. p. 357-385.
9. Penning L. Acceleration injury of the cervical spine by hypertranslation of the head. Part I. Effect of normal translation of the head on cervical spine motion: a radiological study. *Eur Spine J.* 1992; 1:7–12. [PubMed: 20054940]
10. Grauer JN, Panjabi MM, Cholewicki J, et al. Whiplash produces an S-shaped curvature of the neck with hyperextension at lower levels. *Spine.* 1997; 22:2489–2494. [PubMed: 9383854]
11. Ito S, Ivancic PC, Panjabi MM, et al. Soft tissue injury threshold during simulated whiplash: a biomechanical investigation. *Spine.* 2004; 29:979–987. [PubMed: 15105668]
12. Ivancic PC, Sha D. Comparison of the whiplash injury criteria. *Accid Anal Prev.* 2010; 42:56–63. [PubMed: 19887145]
13. Kaneoka K, Ono K, Inami S, et al. Motion analysis of cervical vertebrae during whiplash loading. *Spine.* 1999; 24:763–769. [PubMed: 1022526]
14. Winkelstein BA, Nightingale RW, Richardson WJ, et al. The cervical facet capsule and its role in whiplash injury: a biomechanical investigation. *Spine.* 2000; 25:1238–1246. [PubMed: 10806500]

15. Stemper BD, Yoganandan N, Pintar FA. Effects of abnormal posture on capsular ligament elongations in a computational model subjected to whiplash loading. *J Biomech.* 2005; 38:1313–1323. [PubMed: 15863116]
16. Ivancic PC, Ito S, Tominaga Y, et al. Effect of rotated head posture on dynamic vertebral artery elongation during simulated rear impact. *Clin Biomech (Bristol, Avon).* 2006; 21:213–220.
17. Siegmund GP, Davis MB, Quinn KP, et al. Head-turned postures increase the risk of cervical facet capsule injury during whiplash. *Spine.* 2008; 33:1643–1649. [PubMed: 18594456]
18. Bostrom O, Fredriksson R, Haland Y, et al. Comparison of car seats in low speed rear-end impacts using the BioRID dummy and the new neck injury criterion (NIC). *Accid Anal Prev.* 2000; 32:321–328. [PubMed: 10688488]
19. Siegmund GP, Heinrichs BE, Chimich DD, et al. Variability in vehicle and dummy responses in rear-end collisions. *Traffic Inj Prev.* 2005; 6:267–277. [PubMed: 16087468]
20. Ivancic PC, Coe MP, Ndu AB, et al. Dynamic mechanical properties of intact human cervical spine ligaments. *Spine J.* 2007; 7:659–665. [PubMed: 17998125]
21. Siegmund GP, Myers BS, Davis MB, et al. Mechanical evidence of cervical facet capsule injury during whiplash: a cadaveric study using combined shear, compression, and extension loading. *Spine.* 2001; 26:2095–2101. [PubMed: 11698885]
22. NHTSA. Federal motor vehicle standard No. 202. Code of Federal Regulations, Section 571.21. 1969
23. Minton R, Murray P, Stephenson W, et al. Whiplash injury--are current head restraints doing their job? *Accid Anal Prev.* 2000; 32:177–185. [PubMed: 10688474]
24. Morris AP, Thomas P. Neck injuries in the UK co-operative crash injury study. Society of Automotive Engineers. 1996 Paper No. 962433.
25. Olney DB, Marsden AK. The effect of head restraints and seat belts on the incidence of neck injury in car accidents. *Injury.* 1986; 17:365–367. [PubMed: 3818065]
26. Chapline JF, Ferguson SA, Lillis RP, et al. Neck pain and head restraint position relative to the driver's head in rear-end collisions. *Accid Anal Prev.* 2000; 32:287–297. [PubMed: 10688485]
27. O'Neill B, Haddon W Jr, Kelley AB, et al. Automobile head restraints--frequency of neck injury claims in relation to the presence of head restraints. *Am J Public Health.* 1972; 62:399–406. [PubMed: 5011172]
28. Jakobsson L, Lundell B, Norin H, et al. WHIPS--Volvo's Whiplash Protection Study. *Accid Anal Prev.* 2000; 32:307–319. [PubMed: 10688487]
29. Viano DC, Olsen S. The effectiveness of active head restraint in preventing whiplash. *J Trauma.* 2001; 51:959–969. [PubMed: 11706347]
30. Farmer CM, Wells JK, Lund AK. Effects of head restraint and seat redesign on neck injury risk in rear-end crashes. *Traffic Inj Prev.* 2003; 4:83–90. [PubMed: 16210192]
31. Kullgren, A.; Krafft, M. Gender analysis on whiplash seat effectiveness - Results from real-world crashes. IRCOBI Conference. IRCOBI Secretariat; Bron, France. 2010. p. 17-28.
32. Jakobsson, L.; Norin, H. AIS1 Neck Injury Reducing Effect of WHIPS (Whiplash Protection System). IRCOBI Conference on Biomechanics of Impacts; 2004. p. 297-305.
33. Taylor JR, Twomey LT. Acute injuries to cervical joints. An autopsy study of neck sprain. *Spine.* 1993; 18:1115–1122. [PubMed: 8362316]
34. Lee KE, Davis MB, Winkelstein BA. Capsular ligament involvement in the development of mechanical hyperalgesia after facet joint loading: behavioral and inflammatory outcomes in a rodent model of pain. *J Neurotrauma.* 2008; 25:1383–1393. [PubMed: 19061382]
35. Quinn KP, Winkelstein BA. Cervical facet capsular ligament yield defines the threshold for injury and persistent joint-mediated neck pain. *J Biomech.* 2007; 40:2299–2306. [PubMed: 17141249]
36. Lee KE, Thinnies JH, Gokhin DS, et al. A novel rodent neck pain model of facet-mediated behavioral hypersensitivity: implications for persistent pain and whiplash injury. *J Neurosci Methods.* 2004; 137:151–159. [PubMed: 15262055]
37. Lee KE, Winkelstein BA. Joint distraction magnitude is associated with different behavioral outcomes and substance P levels for cervical facet joint loading in the rat. *J Pain.* 2009; 10:436–445. [PubMed: 19327645]

38. Kallakuri S, Singh A, Lu Y, et al. Tensile stretching of cervical facet joint capsule and related axonal changes. *Eur Spine J*. 2008; 17:556–563. [PubMed: 18080147]
39. Quinn KP, Dong L, Golder FJ, et al. Neuronal hyperexcitability in the dorsal horn after painful facet joint injury. *Pain*. 2010; 151:414–421. [PubMed: 20739124]
40. Dong L, Winkelstein BA. Simulated whiplash modulates expression of the glutamatergic system in the spinal cord suggesting spinal plasticity is associated with painful dynamic cervical facet loading. *J Neurotrauma*. 2011; 27:163–174. [PubMed: 19772459]
41. Quinn KP, Bauman JA, Crosby ND, et al. Anomalous fiber realignment during tensile loading of the rat facet capsular ligament identifies mechanically induced damage and physiological dysfunction. *J Biomech*. 2010; 43:1870–1875. [PubMed: 20381048]
42. Lu Y, Chen C, Kallakuri S, et al. Neural response of cervical facet joint capsule to stretch: a study of whiplash pain mechanism. *Stapp Car Crash J*. 2005; 49:49–65. [PubMed: 17096268]
43. Lu Y, Chen C, Kallakuri S, et al. Development of an in vivo method to investigate biomechanical and neurophysiological properties of spine facet joint capsules. *Eur Spine J*. 2005; 14:565–572. [PubMed: 15690211]
44. Quinn KP, Lee KE, Ahaghotu CC, et al. Structural changes in the cervical facet capsular ligament: potential contributions to pain following subfailure loading. *Stapp Car Crash J*. 2007; 51:169–187. [PubMed: 18278597]
45. Dong L, Odeleye AO, Jordan-Sciutto KL, et al. Painful facet joint injury induces neuronal stress activation in the DRG: implications for cellular mechanisms of pain. *Neurosci Lett*. 2008; 443:90–94. [PubMed: 18675314]
46. Winkelstein BA, Santos DG. An intact facet capsular ligament modulates behavioral sensitivity and spinal glial activation produced by cervical facet joint tension. *Spine*. 2008; 33:856–862. [PubMed: 18404104]
47. Dong, L.; Winkelstein, BA. Injection of Ketorolac Attenuates Joint-Mediated Neck Pain Through the EP2 Prostaglandin Receptor. Annual Meeting of the Society for Neuroscience; San Diego, USA. 2010.
48. Bogduk N. The clinical anatomy of the cervical dorsal rami. *Spine*. 1982; 7:319–330. [PubMed: 7135065]
49. Barnsley L, Lord S, Wallis B, et al. False-positive rates of cervical zygapophysial joint blocks. *Clin J Pain*. 1993; 9:124–130. [PubMed: 8358135]
50. Lord SM, Barnsley L, Wallis BJ, et al. Chronic cervical zygapophysial joint pain after whiplash. A placebo-controlled prevalence study. *Spine*. 1996; 21:1737–1745. [PubMed: 8855458]
51. Barnsley L, Lord SM, Wallis BJ, et al. The prevalence of chronic cervical zygapophysial joint pain after whiplash. *Spine*. 1995; 20:20–25. [PubMed: 7709275]
52. Lord SM, Barnsley L, Wallis BJ, et al. Third occipital nerve headache: a prevalence study. *J Neurol Neurosurg Psychiatry*. 1994; 57:1187–1190. [PubMed: 7931379]
53. Cusick JF, Pintar FA, Yoganandan N. Whiplash syndrome: kinematic factors influencing pain patterns. *Spine*. 2001; 26:1252–1258. [PubMed: 11389392]
54. Pearson AM, Ivancic PC, Ito S, et al. Facet joint kinematics and injury mechanisms during simulated whiplash. *Spine*. 2004; 29:390–397. [PubMed: 15094535]
55. Lord SM, Barnsley L, Wallis BJ, et al. Percutaneous radio-frequency neurotomy for chronic cervical zygapophyseal-joint pain. *N Engl J Med*. 1996; 335:1721–1726. [PubMed: 8929263]
56. McDonald GJ, Lord SM, Bogduk N. Long-term follow-up of patients treated with cervical radio frequency neurotomy for chronic neck pain. *Neurosurgery*. 1999; 45:61–68. [PubMed: 10414567]
57. Govind J, King W, Bailey B, et al. Radiofrequency neurotomy for the treatment of third occipital headache. *J Neurol Neurosurg Psychiatr*. 2003; 74:88–93. [PubMed: 12486273]
58. Barnsley L. Percutaneous radiofrequency neurotomy for chronic neck pain: outcomes in a series of consecutive patients. *Pain Med*. 2005; 6:282–286. [PubMed: 16083457]
59. Panjabi MM, Ito S, Pearson AM, et al. Injury mechanisms of the cervical intervertebral disc during simulated whiplash. *Spine*. 2004; 29:1217–1225. [PubMed: 15167661]
60. Nuckley DJ, Konodi MA, Raynak GC, et al. Neural space integrity of the lower cervical spine: effect of normal range of motion. *Spine*. 2002; 27:587–595. [PubMed: 11884906]

61. Svensson MY, Aldman B, Bostrom O, et al. Nerve cell damages in whiplash injuries. Animal experimental studies. *Orthopade*. 1998; 27:820–826. [PubMed: 9894236]
62. Aldman, B. An analytical approach to the impact biomechanics of head and neck injury. Proceedings of the 39th American Association for Automotive Medicine Conference; Des Plaines, USA. 1986. p. 439-461.
63. Eichberger A, Darok M, Steffan H, et al. Pressure measurements in the spinal canal of post-mortem human subjects during rear-end impact and correlation of results to the neck injury criterion. *Accid Anal Prev*. 2000; 32:251–260. [PubMed: 10688481]
64. Hauser V, Zangger P, Winter Y, et al. Late sequelae of whiplash injury with dissection of cervical arteries. *Eur Neurol*. 2010; 64:214–218. [PubMed: 20720428]
65. Seric V, Blazic-Cop N, Demarin V. Haemodynamic changes in patients with whiplash injury measured by transcranial Doppler sonography (TCD). *Coll Antropol*. 2000; 24:197–204. [PubMed: 10895546]
66. Chung YS, Han DH. Vertebrobasilar dissection: a possible role of whiplash injury in its pathogenesis. *Neurol Res*. 2002; 24:129–138. [PubMed: 11877895]
67. Pollanen MS, Deck JH, Blenkinsop B. Injury of the tunica media in fatal rupture of the vertebral artery. *Am J Forensic Med Pathol*. 1996; 17:197–201. [PubMed: 8870868]
68. Taneichi H, Suda K, Kajino T, et al. Traumatically induced vertebral artery occlusion associated with cervical spine injuries: prospective study using magnetic resonance angiography. *Spine*. 2005; 30:1955–1962. [PubMed: 16135985]
69. Brault JR, Siegmund GP, Wheeler JB. Cervical muscle response during whiplash: evidence of a lengthening muscle contraction. *Clin Biomech (Bristol. Avon)*. 2000; 15:426–435.
70. Macpherson PC, Schork MA, Faulkner JA. Contraction-induced injury to single fiber segments from fast and slow muscles of rats by single stretches. *Am J Physiol*. 1996; 271:C1438–C1446. [PubMed: 8944625]
71. McCully KK, Faulkner JA. Injury to skeletal muscle fibers of mice following lengthening contractions. *J Appl Physiol*. 1985; 59:119–126. [PubMed: 4030553]
72. Scott S, Sanderson PL. Whiplash: a biochemical study of muscle injury. *Eur Spine J*. 2002; 11:389–392. [PubMed: 12194002]
73. Heikkila H, Astrom PG. Cervicocephalic kinesthetic sensibility in patients with whiplash injury. *Scand J Rehabil Med*. 1996; 28:133–138. [PubMed: 8885035]
74. Loudon JK, Ruhl M, Field E. Ability to reproduce head position after whiplash injury. *Spine*. 1997; 22:865–868. [PubMed: 9127919]
75. Madeleine P, Prietzel H, Svarrer H, et al. Quantitative posturography in altered sensory conditions: a way to assess balance instability in patients with chronic whiplash injury. *Arch Phys Med Rehabil*. 2004; 85:432–438. [PubMed: 15031829]
76. Antonaci F, Bulgheroni M, Ghirmai S, et al. 3D kinematic analysis and clinical evaluation of neck movements in patients with whiplash injury. *Cephalalgia*. 2002; 22:533–542. [PubMed: 12230595]
77. Panjabi MM. A hypothesis of chronic back pain: ligament subfailure injuries lead to muscle control dysfunction. *Eur Spine J*. 2006; 15:668–676. [PubMed: 16047209]
78. Solomonow M, Zhou BH, Harris M, et al. The ligamento-muscular stabilizing system of the spine. *Spine*. 1998; 23:2552–2562. [PubMed: 9854754]
79. Anderson JS, Hsu AW, Vasavada AN. Morphology, architecture, and biomechanics of human cervical multifidus. *Spine*. 2005; 30:E86–E91. [PubMed: 15706328]
80. Winkelstein BA, McLendon RE, Barbir A, et al. An anatomical investigation of the human cervical facet capsule, quantifying muscle insertion area. *J Anat*. 2001; 198:455–461. [PubMed: 11327207]
81. Siegmund GP, Blouin JS, Carpenter MG, et al. Are cervical multifidus muscles active during whiplash and startle? An initial experimental study. *BMC Musculoskelet Disord*. 2008; 9:80. [PubMed: 18534030]
82. Graven-Nielsen, T.; Curatolo, M.; Mense, S. Central sensitization, referred pain, and deep tissue hyperalgesia in musculoskeletal pain. In: Flor, H.; Kalso, E.; Dostrovsky, JO., editors. Proceedings of the 11th World Congress on Pain; Seattle: IASP Press; 2006. p. 217-230.

83. Ronnen HR, de Korte PJ, Brink PR, et al. Acute whiplash injury: is there a role for MR imaging?-- a prospective study of 100 patients. *Radiology*. 1996; 201:93–96. [PubMed: 8816527]
84. Voyvodic F, Dolinis J, Moore VM, et al. MRI of car occupants with whiplash injury. *Neuroradiology*. 1997; 39:35–40. [PubMed: 9121646]
85. Sterling M, Jull G, Kenardy J. Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. *Pain*. 2006; 122:102–108. [PubMed: 16527397]
86. Carroll LJ, Cassidy JD, Cote P. The role of pain coping strategies in prognosis after whiplash injury: Passive coping predicts slowed recovery. *Pain*. 2006; 124:18–26. [PubMed: 16644133]
87. Sullivan MJ, Thibault P, Simmonds MJ, et al. Pain, perceived injustice and the persistence of post-traumatic stress symptoms during the course of rehabilitation for whiplash injuries. *Pain*. 2009; 145:325–331. [PubMed: 19643543]
88. Cassidy JD, Carroll LJ, Cote P, et al. Effect of eliminating compensation for pain and suffering on the outcome of insurance claims for whiplash injury. *N Engl J Med*. 2000; 342:1179–1186. [PubMed: 10770984]
89. Sterling M, Jull G, Vicenzino B, et al. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain*. 2003; 104:509–517. [PubMed: 12927623]
90. Imbe H, Iwai-Liao Y, Senba E. Stress-induced hyperalgesia: animal models and putative mechanisms. *Front Biosci*. 2006; 11:2179–2192. [PubMed: 16720304]
91. Kuehl LK, Michaux GP, Richter S, et al. Increased basal mechanical pain sensitivity but decreased perceptual wind-up in a human model of relative hypocortisolism. *Pain*. 2010; 149:539–546. [PubMed: 20381248]

Table 1

Current whiplash injury models and their development state.

Development State	Zygapophysial joint	Dorsal root ganglion	Muscle	Vertebral artery	Spinal ligaments	Disc rim lesion
Theoretical Model	✓	✓	✓	✓	✓	✓
Cadaver/Volunteer						
Injury demonstrated	✓	✗	✓	✓	✓	✓
Animal Model						
Injury produced	✓	✓	✓	✗	✗	✗
Nociception produced	✓	✗	✓	✗	✗	✗
Patient						
Valid diagnosis	✓	✗	✗	✗	✗	✗
Effective treatment	✓	✗	✗	✗	✗	✗

✓ developed; ✗ not developed; NA: not applicable.